BULLETIN

of the

ONTARIO COLLEGE OF PHARMACY

Vol. III, No. 5 | TORONTO, Ontario | November, 1954
H. J. Fuller, Editor

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The Ontario College of Pharmacy is the pharmaceutical licensing body for the Province of Ontario, Canada. All pharmacists licensed in Ontario are *IPSO FACTO* members of the College.

The majority of contributors to the Bulletin are members of the Faculty of Pharmacy, University of Toronto. However, contributions are welcomed from all members of the College.

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AN EXPLANATION OF THE NEW REGULATIONS THE OPIUM AND NARCOTIC DRUG ACT

In this Act where the word Drug appears it means Narcotic.

1. There are 3 categories into which Narcotics can be classified.
   (1) Drug or Narcotic = Straight Drug.
   (2) Narcotic Product = A Narcotic or Narcotics in combination with one or more medicinal ingredients other than Narcotic in a recognized therapeutic dose.
   Ex. — Gall & Opium Ointment.
   (3) Oral prescription Narcotic Product =
   (1) Two or more medicinal ingredients other than Narcotics in a recognized therapeutic dose — Ex - 282, 292, cheracol cosanyl, terpo dionin.
   (11) Is not intended for parenteral use.

2. Labels on Narcotics, Narcotic products and Oral Prescription Narcotic Products will bear the letter N and will be labelled with the net contents and other medicinal ingredients per unit. Containers must be sealed. This does not apply to prescriptions or to those narcotic products which may be sold without prescription such as A.P.C. with Codiene 1/8 gr.

3. On receipt of any Narcotic or Narcotic Product an entry must be made in your record of purchases. This includes even A.P.C. with Codiene Gr. 1/8 properly labelled for sale without prescription.

4. On dispensing a prescription a record of sale is required in your narcotic register for Narcotics and Narcotic Products **but not for Oral Prescription Narcotic Products.** The prescription number is now required in the Narcotic Register.

5. In medication containing **One** Narcotic in combination with two or more non narcotic medicinal substances in recognized dosage and not in a form intended for parenteral administration and when the pharmacist uses a supply of narcotic such as Codiene or Morphine he is required to make an entry in the Narcotic register of sales to account for the narcotic utilized in this case—

Ex.—Phenacetin gr. ii
Cod. Phos. gr. ½
Acetylsalicylic Acid gr. ii
Caffeine gr. i, Ft. Cap #1 Mitte x

There will be an entry in sales register to account for the 5 grains of codiene phos. used.

6. In Oral prescription Narcotic Products received over the phone, the pharmacist must satisfy himself that the person giving the prescription is a Physician, Dentist or Veterinary Surgeon. The onus is on the Pharmacist.

7. When taken over the phone reduce to writing immediately Oral Narcotic Prescription Narcotic Products in the form of a prescription and put the name of the pharmacist who receives it on the prescription.

8. Each Narcotic or Narcotic Product Prescription must be numbered in sequence, dated and placed on a separate file for that purpose only.

9. All Narcotic and Narcotic Products except Oral Prescription Narcotic Products must be kept under lock and key.

(continued on page 71)

THE SUPPLY OF GRADUATES IN PHARMACY

Dr. F. N. Hughes

From time to time rather fantastic rumours reach our ears respecting the number of students entering Pharmacy and the distribution of current graduates among the various branches of the profession. For example, we were quite surprised to "learn" this summer that only 17 students were going to be enrolled in the first year. Actually 101 were registered, in addition to 5 new students entering the second year holding B.A. or B.Sc. degrees. On several occasions we have been advised that over 50% of the graduates of the four-year course were not entering retail pharmacy. Actually over 80% have consistently been entering retail practice.

It seems timely, therefore, to set forth the true situation respecting the present and future supply of graduates in pharmacy. Some aspects are very encouraging while others are cause for concern. These latter, however, can most certainly be altered favourably if all of us do our part.

Between 1948 and 1951 inclusive the number entering the first year of the course leading to the degree of Bachelor of Science in Pharmacy was of necessity restricted to 25 or 50 due to the concurrent two-year course. Consequently during this four-year period a large number of applicants were unable to gain admittance. Some registered as apprentices but many turned to some other vocation. As a consequence Pharmacy gained the reputation of being a difficult course to enter. There is no way of knowing how much effect this has had upon the number of applications during the past three years, but we do know it has had some influence which is just now being overcome. First-year enrolments since 1948 have been:

1948—25; 1949—50; 1950—50; 1951—50;
1952—120 (56 apprentices, 64 directly from school)
1953—84 (15 apprentices, 69 directly from school)
1954—101 (5 apprentices, 96 directly from school)

It is evident from the much larger number admitted in September, 1954, that there is an increasing interest in Pharmacy due to the greater interest taken by pharmacists in vocational guidance in some centres combined with the widespread use of the Foundation filmstrip "Careers in Canadian Pharmacy".

However, there is another aspect which is causing concern. Prior to the war, between 1936 and 1940, 74% of the students came from outside the Greater Toronto area. Between 1950 and 1953 only 44% came from the extra-Toronto part of the province. Further, while 13.6% of students in the prewar five years were resident in the cities of Hamilton, Ottawa, London or Windsor, only 8% came from these centres in the 1950-53 period. A summary of the geographic

distribution follows:

	Toronto Area	Hamilton, Ottawa, Etc.	Others
1936-40	26%	13.6%	60.4%
1950-53	55.8%	7.7%	36.5%

This is not a healthy situation in any profession, when it is recognized that graduates tend either to return to their home district or to remain in the largest centre in the province. Very rarely does a Toronto student go outside of the area to practice. Consequently there is a danger that some parts of the province will be left ultimately with no pharmaceutical service of any kind. And, in the meantime, retail pharmacies and hospitals in some cities and towns are suffering a serious shortage of qualified assistance.

Furthermore, with the increase in population which has occurred in Ontario since 1941, a total of 100 graduates is not adequate to meet genuine demand even if they are well distributed. Consequently two problems exist: (1) to increase total intake of students up to at least 125, and (2) to increase the proportion of students from the province outside of the Toronto area.

The first of these, is, we believe, in process of being solved satisfactorily. The marked increase in enrolment this year is an indication that the flow of students into Pharmacy may well have begun again. Thus, if attention can be given to the second problem both may well be solved simultaneously.

The solution to this problem lies with the pharmacists in every centre of Ontario. In some districts the pharmacists have taken active steps to co-operate with secondary schools in guidance programmes. Local practitioners have addressed students making good use of the Foundation filmstrip "Careers in Canadian Pharmacy", which may be borrowed through the Registrar of the Ontario College of Pharmacy. In one district, South Waterloo, the pharmacists have gone a step further and established an annual bursary of $200.00 to assist a deserving student to enter the Faculty of Pharmacy. Other centres are considering similar action. In most areas of Ontario, pharmacists could do this with little cost to themselves individually, but with much benefit to Pharmacy, not only with respect to stepping up the inflow of promising candidates but also through improved local public relations.

The effectiveness of local co-operation with guidance counsellors is already apparent in the enrolment this session. During the past year pharmacists have been active in four centres from which no students came one year ago. In the present class there are 13 registered from these cities. Probably some of these would have entered Pharmacy anyway, but the increase is much too great to be accidental.

Following are some important points to bear in mind when talking to prospective candidates either in groups or individually:

1. There are varied types of positions which are open to graduates in Pharmacy: retail, hospital, manufacturing (production, laboratory control, product development), medical representatives (detailing), government laboratories, armed services (commissioned ranks), research and teaching (these last two require graduate study).

2. A substantial number of women graduates are constantly in demand.

3. Salaries are excellent in all branches; most qualified graduates receive at least $75.00 weekly initially, many start at a higher level.

4. Be completely fair by presenting the advantages **and** the disadvantages of Pharmacy as a career. It is important in this connection to be completely objective and not to permit personal prejudices to colour the presentation to any appreciable degree. Try to have facts which do justice to the over-all situation in the profession. For example, if the pharmacies in your own town are open until 11 p.m., be sure to point out that in some centres they are closed at 6 or 7 p.m.

5. Ascertain the candidate's specific academic strengths and weaknesses and his personal preferences regarding type of work. Academically, he should like and be reasonably proficient in the sciences and mathematics.

6. It should not be overlooked that the present university course in Pharmacy is not, in any sense, a "technical training" but is designed to provide an education for citizenship and the practice of a profession. The curriculum is an excellent course of study for anyone who enjoys the natural sciences. It has the further advantage of practicality in that it offers an education leading to qualification to practise a health profession which can provide a comfortable income throughout life.

F. NORMAN HUGHES

HONOURED

On May 30, 1954, at Purdue University, the Honorary Degree of LL.D. was conferred on Dean F. N. Hughes. In presenting Dean Hughes to the Chancellor of Purdue University, Dean G. L. Jenkins of the School of Pharmacy, testified as follows:

"It is with pleasure that I present Dean Francis Norman Hughes, a Canadian citizen and a graduate from Purdue University with the degree of Bachelor of Science in Pharmacy in 1940. In 1944, he received the M.A. degree from the University of Toronto. Mr. Hughes as a professor and later as dean had led his school, now an integral part of the University of Toronto, to a high position in professional pharmacy education in the Dominion of Canada. As a science editor in professional journalism, as the author of books, as the Secretary of the Canadian Conference of Pharmaceutical Faculties, as a leader in the Canadian Pharmaceutical Association, and in other ways, Mr. Hughes has rendered distinguished service to the advancement of his profession and has contributed to improved education, health and welfare in his country.

Because of his achievement and acting for the faculty and Board of Trustees of Purdue University, I request that the degree Doctor of Laws be now conferred upon him."

LEARNING FOR THINKING

"It is on the side of its dealings with the whole complex problem of human relations that formal education is today found wanting. It has been spectacularly successful in penetrating into the secrets of the processes of nature. It has been amazingly effective in exploiting these through techniques. It has only begun to falter at the social level where the human factor enters more directly into the picture. It is, then, on the side of the humane and social studies, where liberal education carries the heaviest responsibilities, that the weakness lies. . . . "

(continued on page 82)

AUTONOMIC DRUGS

Part VI - Adrenergic Blocking Agents, concluded.

Dr. G. R. Paterson

A number of synthetic drugs with adrenergic blocking action have been developed and shown to have at least potential value in such clinical entities as hypertension and peripheral vascular disease.

Tolazoline Hydrochloride, U.S.P. (Benzazoline Hydrochloride, Priscol, Priscoline) is water - soluble, so may be administered orally or parenterally. It is a vasodilator and has been used for the relief of angiospasm, Buerger's disease, Reynaud's disease and in the treatment of ulcers caused by poor circulation.

Phentolamine Methanesulfonate, U.S.P. (Regitine, Rogitine is useful in the treatment of peripheral vascular disease and in hypertensive emergencies. It is also used as a diagnostic agent for pheochromocytoma (a cell tumour of the adrenal medulla) because it blocks the pressor action of epinephrine. It also prevents paroxysmal attacks in such patients prior to surgery. It is administered intravenously or intramuscularly.

Hydrallazine (Hydralazine Hydrochloride, N.N.R., Apresoline Hydrochloride) is reported to possess not ony the ability to reduce blood pressure but also the property of increasing the blood flow to the kidneys. It has been used in treating hypertensive individuals.

Dibenamine differs from the other adrenergic blocking agents in that it produces a slowly developing and prolonged adrenergic blockade not overcome by massive dosages of epinephrine. Its irritating qualities (because of its close chemical relationship to the nitrogen mustards) makes intravenous administration necessary. Its most successful use thus far has been in the treatment of peripheral arterial embolism and Reynaud's disease. The many side effects of the drug have restricted its clinical use but it is extremely useful in experimental pharmacology.

Piperoxan Hydrochloride, N.N.R. (Benodaine Hydrochloride) is most useful in the diagnosis of pheochromocytoma, which causes increased secretion of epinephrine and thus a state of hypertension. Within a few seconds of injection, the drug causes in such patients a significant drop in blood pressure. The original pressure is regained in 15 - 20 minutes. The drop in pressure is due to the drug's anti-epinephrine activity and serves to diagnose the cause of the hypertension. Surgery is then indicated. **Prosympal** is related chemically to Piperoxan and has been reported as possessing a relaxing effect in angina pectoris.

G. R. PATERSON.

(continued from page 66)

10. **No repeats** on any Narcotic.
11. In the case of a pharmacist wishing to manufacture a narcotic product, written permission to do so is required and he must submit the formula to the Department and keep records.
12. The approval of the Minister is required for the transfer of or to dispose of Narcotics other than on prescription.

T. E. E. GREENFIELD

PHARMACY or DEPARTMENT STORE

In a recent issue of a state pharmaceutical journal a student at a college of pharmacy decried the trend of retail pharmacies toward the department store variety rather than the practice of pharmacy. We have many times deplored this trend in so many retail establishments. In many instances one enters a so-called pharmacy only to be confronted with myriads of merchandise such as clocks, toys, beach equipment and the like. In order to find the prescription department one must almost literally wade through hundreds of items completely foreign to pharmacy. In some few instances when a customer finally finds the prescription department it is a well-kept and professional looking section. However, too often, the contrary is true and it is a "hole-in-the-wall" operation which is maintained only so that the store can be legally called a drug store.

It is this "department store attitude" which seriously affects the profession and does more than any other really known factor to lower the prestige of pharmacy in the eyes of the public and the medical profession.

If one who is only a student is alert enough to recognize this weakness of pharmacy, is it any wonder that we encounter difficulties in encouraging promising young people to enter the profession? One glance at some of the drug-department stores is sufficient to convince them that they could do better by majoring in merchandising and not be bothered with the courses in pharmacy and with state board examinations.

If we are really to give pharmacy the professional air it so rightfully deserves it is time that such an attitude be adopted and the "department" store attitude be submerged. Pharmacists would often do well to listen to the young people entering the profession. A little more idealism would do the whole area of pharmacy much good. Of cynicism and materialistic reasoning we have in pharmacy more than plenty.

Madeline Oxford Holland, D.Sc., Editor, The American Professional Pharmacist.
Reprinted, with permission, from the August 1954 American Professional Pharmacist.

DO YOU KNOW

That the Canadian Foundation for the Advancement of Pharmacy has provided over $7,000.00 to assist pharmaceutical education in Ontario during the past year while Ontario pharmacists contributed less than $3,500.00 to the Foundation? Have you sent in your annual contribution yet?

DO YOU KNOW

That the filmstrip "Careers in Canadian Pharmacy" is the only visual aid available to assist vocational guidance counsellors in the presentation of Pharmacy to secondary school students? It was prepared at a cost of $2,000.00 by the Canadian Foundation for the Advancement of Pharmacy. Have you sent in your cheque yet?

F. NORMAN HUGHES

ANTIBIOTICS

Resistant Strains and Their Significance in Antibiotic Therapy

Dr. Ross M. Baxter

In a preceding section entitled "Antibiotic Spectra", it was indicated that broad spectrum antibiotics act by blocking some metabolic reaction which is essential to a relatively large number of microorganisms whereas the narrow spectrum antibiotics block a metabolic reaction which is essential to a small number of microorganisms. It may also be stated that the effectiveness of an antibiotic depends to a considerable extent on the essentiality of the metabolic reaction of the microorganisms, which it blocks.

It has been shown that microorganisms adapt themselves to certain antibiotics and thus are able to develop and multiply in the presence of the chemical. These microorganisms which are no longer affected by the antibiotic are designated as **resistant strains** and in certain cases can create a problem in the selection of an effective agent for treating infections due to resistant strains.

The manner in which these resistant strains develop is in general by adaptation of the microorganisms resulting in the emergence of variants or mutants.

The emergence of resistant strains may be as a result of two factors. (1) The antibiotic has suppressed the growth of the rapidly growing, antibiotic-sensitive portion of the bacterial population. This may in turn allow the slower growing segment of the same bacterial population to develop since the inhibitory effect of the rapidly growing bacterial population has been removed. This slower growing group may be relatively resistant to the antibiotic and thus continue to develop in its presence. This variation in susceptibility of the individuals of a particular bacterial population (e.g. Staphlococcus aureus etc.) is not unique to bacteria or microorganisms. We are all cognizant of the great individual variation in the human response to certain drugs and the fact that certain patients may become increasingly resistant to the effect of a certain drug necessitating an increased dosage schedule or changing to another therapeutic agent. Thus we may then conclude the discussion of this factor by saying that in any infection due primarily to a single organism there are in the area of the infection a large population of the particular organism. One part of the population may be particularly sensitive to the antibiotic whereas the remainder and usually a much smaller proportion of the population will exhibit a greater resistance to the chemical used to treat the infection. (2) If in a particular infection all of the members of the population are sensitive to the antibiotic the infection is usually brought under control due to the

eradication of the infecting organisms. However in certain cases the antibiotic may either passively or actively produce changes in the organism resulting in the development of organisms which can flourish in the presence of the antibiotic. When the antibiotic causes the development of resistant strains indirectly or passively it is usually due to an adaption of the metabolic processes of the organisms to utilize nutrients in a manner which circumvents the particular reaction which has been blocked or inhibited by the antibiotic. Active participation of the anti-infective agent in developing resistance is thought to be the result of an anti-mitotic action similar perhaps to that of colcichine and podophyllum which causes an alteration in the **genes** (metabolic regulatory factors) resulting in a strain whose metabolic processes are sufficiently altered that the growth of the organism is no longer affected by the chemical used to combat the infection.

An understanding of the manner in which resistant strains develop, the effect of their development on the course of a particular infection and succeeding infections due resistant organisms is of prime importance to the physician and also to the pharmacist although in a more indirect manner. By judicious choice of antibiotics and by administration in optimum amounts the development of resistant strains may be prevented or at least curtailed. The manner in which this may be carried out will be discussed in a future article.

R. M. BAXTER.

HOSPITAL PHARMACISTS' ACTIVITIES

Canadian Hospital Pharmacists travelled to Atlantic City, Storrs, Connecticut, and Boston during the summer to attend refresher courses and meetings and obtain up-to-date information on the many facets of hospital pharmacy practice. Hospital administrators, leading clinicians in the various medical fields, and hospital pharmacists participated in the programs which included such topics as "Pharmacy Administration and Policies", "Bulk Compounding—Factors Influencing the Pharmacy Policy", the "Clinical Use of Electrolytes", "Hormones and Their Effective Use Today", "Pharmaceutical Properties of Isotopes", "Preservatives for Parenterals", "Preliminary Evaluation of a New Iodine Germicide" and "The International Pharmacopoeia—Its Evolution and Its Role in World Health". Time was also provided for informal discussions, in groups of ten or fifteen, under the leadership of members capable of bringing personal experience to the specific problem at hand. Here each hospital pharmacist had an opportunity to obtain practical help and learn of sources of information which could be directly applied to situations in his own hospital.

The individual hospital pharmacist who has been fortunate enough to attend these institutes and meetings has enjoyed a stimulating experience and returned to his hospital filled with enthusiasm for his profession and the pharmaceutical and hospital associations which have helped him to gain new knowledge with which to lighten his daily tasks. During the coming months he will have an opportunity to share this knowledge with his colleagues in the local branch of the Canadian Society of Hospital Pharmacists, such as the Hospital Pharmacy Section meeting of the Ontario Hospital Association Convention to be held at the Royal York Hotel on October 26th, and regular monthly meetings.

This concept of public service is only natural for hospital pharmacists because of the environment in which they work and serve, the hospital, whose primary function is better patient care. In 1955, the Provincial branches of the Canadian Society of Hospital Pharmacists will devote the program of their April meetings to a discussion of Minimum Standards for Pharmacies in Hospitals and the Hospital Accreditation Program. At the Canadian Pharmaceutical Convention in Halifax, at the annual meeting of the Practising Pharmacists' Advisory Council, an invitation was extended to members of all branches of Pharmacy to attend these branch meetings of the Canadian Society of Hospital Pharmacists and to visit the Pharmacy Department in local hospitals on National Hospital Day, May 12th. Canadian Hospital Pharmacists joined with other Canadian pharmacists in supporting the Canadian Foundation for the Advancement of Pharmacy by the presentation of their contribution at the annual meeting of the Foundation at Halifax this year. Plans are underway for a Canadian Hospital Pharmacy Institute to be held in Vancouver on the Saturday and Sunday preceding the Canadian Pharmaceutical Convention in August of next year.

These are the pharmacists to whom the Canadian Pharmaceutical Association has granted representation on the Council along with the Canadian Conference of Pharmaceutical Faculties. Their numbers may be few, but their enthusiasm is great. Dr. Albert W. Snoke, Director of Grace-New Haven Community Hospital and Professor of Public Health at Yale University, New Haven, Connecticut, in speaking on "The Administrator's Viewpoint on the Pharmacy" indicated that "what is good for the patient is good for the hospital and, in turn, good for the pharmacist". It is to be hoped that what is good for Canadian Hospital Pharmacists will be good for Canadian Pharmacy.

I. E. STAUFFER

PROMOTIONS - JULY 1, 1954

Dr. G. C. Walker was promoted from Associate Professor of Pharmacy to Professor of Pharmacy. Dr. Walker is the genial secretary of the Canadian Conference of Pharmaceutical Faculties, and secretary of the Association of the Teaching Staff, University of Toronto.

Dr. R. M. Baxter was promoted from Assistant Professor of Materia Medica to Associate Professor of Materia Medica. Dr. Baxter is the editor of Scientific News and Seminar of the Canadian Pharmaceutical Journal.

Dr. G. R. Paterson was promoted from Assistant Professor of Pharmaceutical Chemistry to Associate Professor of Pharmaceutical Chemistry. Dr. Paterson is the editor of the Conference Section of the Canadian Conference of Pharmaceutical Faculties of the Canadian Pharmaceutical Journal. On June 18, 1954, Professor Paterson was granted the Ph. D. degree by the University of Wisconsin. His Thesis was "Studies on Verbenalin and Verbenalol".

SUBLINGUAL ADMINISTRATION

(Part of an experimental thesis conducted under the direction of Dr. G. C. Walker, Professor of Pharmacy, submitted in partial fulfillment of the degree of Bachelor of Science in Pharmacy by Robert Lawrence Hooper, Toronto, Ontario, April, 1953).

Introduction

Since the introduction into chemotherapy of many drugs which are inactivated in the intestines it has been necessary to devise a suitable form for the administration of these drugs. Intravenous and intramuscular injections are usually the methods of choice for rapidly reaching a high therapeutic blood level. Among the less common routes of administration is sublingual therapy. Utmost confidence and dubiousness, both have shrouded the efficacy of sublingual administration. It is the purpose then of this thesis to outline the position and scope of sublingual administration as it exists today. The experimental section will contain details on a study of a suitable base for sublingual tablets.

Technique and Rationale

Walton and Lacey (7) found that by sublingual application, strong aqueous solutions were consistently more effective than powders of the drug. This was evidently due to the time required for the powders to go into solution. This difference, of course, would not be manifest by tablets with a slow, even breakdown. Thus there is no evidence that the tablet form of administration is any more efficient than the solution form except in the matter of convenience to the patient. The tablet may be placed under the tongue and the patient instructed not to eat, drink, talk, smoke, chew or in any way hasten tablet disintegration. Absorption from this location is usually complete in about thirty minutes (1).

If the tablet is placed in the buccal pouch, a longer period of time is required for absorption, forty-five to sixty minutes. The patient may talk but should refrain from eating, drinking etc., while the tablet is in this position.

Sublingual, rather than buccal administration is to be preferred in patients who wear dentures. Administration is more convenient when the patient is reading, listening to the radio, commuting, or some such pastime at which he is quiet, but not on retiring because the tablet may slip into the larynx during sleep.

When the tablet is placed under the tongue, the drug is absorbed directly into the systemic circulation by way of the sublingual blood vessels and lymphatics thus by-passing the liver.

Advantages

Aside from the fact that there is a great difference in the ease and rapidity with which various agents are admitted to the circulation through the oral membrane, the advantages of such a mode of administration are readily evident. This may be very aptly expressed by three "E" 's: Ease of administration, Efficacy and Economy. Patients find sublingual tablets to be more pleasant and more convenient than injections. In wartime and time of accident it is not always possible to administer drugs by injection rapidly or in such a manner as to ensure their sterility. At times it also may not

be possible to administer them orally due to the nature of the medication or the condition of the patient. Thus drugs may be conveniently given by the sublingual route and ready absorption into the blood stream may be obtained without the need for special apparatus or sterilization procedures. Very few drugs, however, are routinely used in this way in regular practice.

Present Status of Sublingual Administration

The sublingual route is not new. Drugs such as nitroglycerine, morphine, and atropine have been administered by this method for many years. As early as 1870, Sir Robert Lauder Brunton used this method of administering nitroglycerine (2). However, due to the variance of drug action and the variance of reports in the literature, a large number of exact experiments on this important question is urgently needed. To illustrate this point we only need to look at the earliest reports regarding sublingual administration and those released as recently as 1942. Paulson, among the first who suggested sublingual therapy, advocated this procedure for the administration of morphine and atropine in emergencies, as well as for other drugs (3).

"The only preparation necessary is rinsing with water if the mouth is dry. A hypodermic tablet, powdered with the point of a penknife on paper creased in the centre and dropped just behind the teeth, the tongue being restored to its normal position, will be absorbed in a few seconds. The full effects of the dose may be absolutely depended on, almost immediately (3)".

Recently there were recommendations both in the United States (4) and in England (5) that morphine be administered sublingually in those wartime emergencies in which hypodermic injections were not possible. The recommendations were challenged (6) and, fortunately, have not been generally accepted. Evidently therefore, there does not exist any clear and general recognition of the scope and limitations of this particular therepeutic technique.

Method and Evaluation of Experimental Work

The effectiveness or ineffectiveness of this technique can be determined easily and, in fact, has been determined for many of the common drugs. Clinical administration of drugs via the sublingual route to afflicted patients has given evidence as to the effectiveness of this type of therapy in many cases. Often however, unreliable impressions have been created due to the mere sublingual administraion of drugs in their ordinary subcutaneous dose, and the only criterion of effectiveness being the comment of patients regarding their subjective sensations. To be certain that a drug is not effective by sublingual administration it might be considered necessary to increase the doses through successive trials after starting with the ordinary subcutaneous dose. This also reduces the hazard of overdose for the human subject. In experimental procedures with human subjects (7) healthy, young men of medium build were chosen. The drugs were held under the tongue for eight to fifteen minutes with conscious efforts to prevent swallowing, whereupon the mouth was thoroughly rinsed with water. The time interval before appearance of effects was calculated from the time the drugs were first placed under the tongue.

A method of preliminary animal experimentation is available also and has proved to be a reliable guide. Dogs can be managed in such a way as to minimize swallowing and, as a further proof for those drugs which are well absorbed, dogs can be used after esophageal operations which completely exclude the possibility of swallowed drugs passing into the stomach or intestine. Also in dogs, fistula, tone changes, blood pressure changes, anaesthesia, excitation and other methods can be used as a suitable means of bioassaying the extent of drug absorption. Without exception, drugs are more readily absorbed from the sublingual area of the dog than from the same area in man (8). Hence a drug which does not penetrate the mucosa of a dog can be applied experimentally to the mucosa of human subjects in relatively large doses with the assurance that effects will not be obtained.

Penetration of drugs through the oral mucosa varies from those few drugs which penetrate readily, to those which penterate only when larger doses are applied and those which seem almost incapable of any significant degree of penetration. Walton (8) finds that penetrability is favoured by a high fat-water distribution coefficient or in a few exceptions by an exceptionally high-fat solubility. Thus within a group of chemically related drugs, absorption properties may be readily predicted and individual absorption behaviour explained on the basis of this correlation.

Drugs Which Penetrate Readily

Organic Nitrates

The most clinically accepted drug for sublingual administration is glyceryl trinitrate. Both it and its higher homologue, erythrityl tetranitrate, which have essentially the same solubility characteristics, readily penetrate the oral mucosa (9,10). Both drugs also possess high distribution coefficients; Krantz and his associates (11) reporting them as 1,820 for glyceryl trinitrate and 290 for erythrityl tetranitrate.

Steroid Hormones

The sublingual or buccal route for administration of steroids has become accepted as a reliable and efficacious mode of treating certain clinical conditions. With the increasing usefulness of the steroids and the advantages to be gained by this method (most steroids in practical doses are either relatively or totally inert when swallowed because they are considerably inactivated by the liver after passage through the portal circulation) it should enjoy increasingly widespread adoption.

Androgens

Testosterone compounds used in solutions of propylene glycol or in compressed tablets have been shown to be effective by sublingual application (12). Methyltestosterone is the most widely employed and most active hormone, being followed by plain testosterone unesterified and testosterone propionate respectively.

Estrogens

Numerous observers have reported the clinical effectiveness of various sublingual administered estrogens (13). Hall (13-a) considered sublingual doses of alpha-estradiol about equal to injected doses. Administration of diethylstilbestrol in propylene glycol indicated that the sublingual doses were about equally effective as swallowed doses and half as effective as intramuscular doses (13-c).

be possible to administer them orally due to the nature of the medication or the condition of the patient. Thus drugs may be conveniently given by the sublingual route and ready absorption into the blood stream may be obtained without the need for special apparatus or sterilization procedures. Very few drugs, however, are routinely used in this way in regular practice.

Present Status of Sublingual Administration

The sublingual route is not new. Drugs such as nitroglycerine, morphine, and atropine have been administered by this method for many years. As early as 1870, Sir Robert Lauder Brunton used this method of administering nitroglycerine (2). However, due to the variance of drug action and the variance of reports in the literature, a large number of exact experiments on this important question is urgently needed. To illustrate this point we only need to look at the earliest reports regarding sublingual administration and those released as recently as 1942. Paulson, among the first who suggested sublingual therapy, advocated this procedure for the administration of morphine and atropine in emergencies, as well as for other drugs (3).

"The only preparation necessary is rinsing with water if the mouth is dry. A hypodermic tablet, powdered with the point of a penknife on paper creased in the centre and dropped just behind the teeth, the tongue being restored to its normal position, will be absorbed in a few seconds. The full effects of the dose may be absolutely depended on, almost immediately (3)".

Recently there were recommendations both in the United States (4) and in England (5) that morphine be administered sublingually in those wartime emergencies in which hypodermic injections were not possible. The recommendations were challenged (6) and, fortunately, have not been generally accepted. Evidently therefore, there does not exist any clear and general recognition of the scope and limitations of this particular therepeutic technique.

Method and Evaluation of Experimental Work

The effectiveness or ineffectiveness of this technique can be determined easily and, in fact, has been determined for many of the common drugs. Clinical administration of drugs via the sublingual route to afflicted patients has given evidence as to the effectiveness of this type of therapy in many cases. Often however, unreliable impressions have been created due to the mere sublingual administration of drugs in their ordinary subcutaneous dose, and the only criterion of effectiveness being the comment of patients regarding their subjective sensations. To be certain that a drug is not effective by sublingual administration it might be considered necessary to increase the doses through successive trials after starting with the ordinary subcutaneous dose. This also reduces the hazard of overdose for the human subject. In experimental procedures with human subjects (7) healthy, young men of medium build were chosen. The drugs were held under the tongue for eight to fifteen minutes with conscious efforts to prevent swallowing, whereupon the mouth was thoroughly rinsed with water. The time interval before appearance of effects was calculated from the time the drugs were first placed under the tongue.

A method of preliminary animal experimentation is available also and has proved to be a reliable guide. Dogs can be managed in such a way as to minimize swallowing and, as a further proof for those drugs which are well absorbed, dogs can be used after esophageal operations which completely exclude the possibility of swallowed drugs passing into the stomach or intestine. Also in dogs, fistula, tone changes, blood pressure changes, anaesthesia, excitation and other methods can be used as a suitable means of bioassaying the extent of drug absorption. Without exception, drugs are more readily absorbed from the sublingual area of the dog than from the same area in man (8). Hence a drug which does not penetrate the mucosa of a dog can be applied experimentally to the mucosa of human subjects in relatively large doses with the assurance that effects will not be obtained.

Penetration of drugs through the oral mucosa varies from those few drugs which penetrate readily, to those which penterate only when larger doses are applied and those which seem almost incapable of any significant degree of penetration. Walton (8) finds that penetrability is favoured by a high fat-water distribution coefficient or in a few exceptions by an exceptionally high-fat solubility. Thus within a group of chemically related drugs, absorption properties may be readily predicted and individual absorption behaviour explained on the basis of this correlation.

Drugs Which Penetrate Readily

Organic Nitrates

The most clinically accepted drug for sublingual administration is glyceryl trinitrate. Both it and its higher homologue, erythrityl tetranitrate, which have essentially the same solubility characteristics, readily penetrate the oral mucosa (9,10). Both drugs also possess high distribution coefficients; Krantz and his associates (11) reporting them as 1,820 for glyceryl trinitrate and 290 for erythrityl tetranitrate.

Steroid Hormones

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However, with a later comparison of the minimum effective dose, both estrogens and stilbestrol were found to be about equally effective by sublingual administration as by injection (13-e).

Anhydrohydroxyprogesterone

Joel (13-b) reported that sublingual doses of anhydrohydroxyprogesterone were approximately one-half the oral dose. However, oral doses are considered to be 5 to 8 times the injected dose. Corner (13-e) states the sublingual dosage to be 4 times the injected dose. Bickers (14) later confirmed the work of Joel, finding that progesterone was equal to or slightly less than the oral dosage.

Desoxycorticosterone Acetate

Administration of desoxycorticosterone acetate sublingually also has received favourable reports clinically (15). Although there is some variance of opinion, the sublingual dosage may be considered to compare favourably with the amount required by intramuscular injection. Corner (13-e) reported that in mild clinical cases a dose equal to or 2 times the intramuscular dose was required and in severe cases 3 to 4 times this dosage was indicated.

Summary

with the exception of estrogens, which appear equally potent sublingually, the average sublingual dose of the steroid hormones is 3 to 4 times the intramuscular dose. Furthermore, it should be noted that the dosage may vary from one individual to another.

Vitamins

The fat soluble vitamins no doubt could be administered by sublingual application, although ordinarily there is no need for administration by this route.

Alkaloids

Apomorphine, although very slightly soluble in fats, is extremely insoluble in water with the result that its distribution coefficient is high (16). Doses about twice that of subcutaneous doses are effective (16). Sublingual administration of this drug is of course not practical.

Nicotine passes through the oral mucosa with considerable ease and promptness (8). Its distribution coefficient is low being decimal 2.6 but it is completely miscible with fat in all proportions. In addition, this alkaloid is unusually alkaline and irritant, the latter feature being possibly an important conditioning factor in its high degree of penetrability. Nicotine is of more toxicologic interest rather than therapeutic.

Cocaine is another drug whose absorption through the oral mucosa is chiefly a matter of toxicologic interest. Its distribution coefficient is relatively high being 32 and its sublingual dosage is twice that of the subcutaneous dose. In human subjects the absorption of cocaine through the more permeable nasal mucosa is well known.

Analeptics

Alpha - (3,4 - dihydroxyphenyl) - beta - isopropylaminoethanol sulphate or isopropylepenephrine is chemically related to epinephrine. As well as exhibiting many marked therapeutic advantages over epinephrine, it is effective sublingually whereas epinephrine is not. The dosage of isopropylepenephrine is 20 to 40 milligrams (18-b).

Drugs Which Do Not Penetrate the Oral Mucosa

Many non-irritant drugs effective in small doses have been claimed to be effective sublingually. But, as previously stated, if they do not exhibit a high distribution coefficient or a high fat solubility, they are not effectively administered in this way and any effects which may have been obtained are due to small amounts having been swallowed.

Morphine Derivatives

Morphine, codeine and dilaudid have low distribution coefficients, less than two, and are very slightly soluble in oil, hence, as might be expected, they do not pass through the oral mucosa to any significant degree (16). Diacetyl morphine in spite of a slightly higher distribution coefficient of 17 was also found to be impracticable administered in this way. The conclusion stands clearly that these opiates cannot be administered by any of the currently used techniques.

Ergot Alkaloids

Ergonovine, possessing a very low distribution coefficient, acts in agreement with the correlation, being ineffective by sublingual application (8). This finding of Walton is in direct contrast to those secured using ergonovine which indicated the effectiveness of its sublingual administration (17) and the occasional practice of administering it in this way in some of the larger obstetric clinics. Walton states that the clinical results must have been due to swallowing.

Further study is required concerning ergotamine. The need for its repeated administration in the management of some migraine cases makes the sublingual method an attractive one. The development of a more readily water-soluble salt of ergotamine would possibly lend itself to routine use in this way.

Autonomic Drugs

Atropine exhibits a low degree of penetrability (8). It is conceivable that among the various synthetic and natural products which have pharmacologic similarity to atropine, some may be found which have an adequate degree of penetrability. No systematic study of this sort has been made.

Barbiturates

Walton found that the sodium salts of two barbiturates, pentobarbital (7) and 1 - methyl - butyl methallyl barbiturate (10) produced promising results in dogs. Nonetheless, in human trials sedative effects were obtained only with 4 grain doses of sodium pentobarbital and this involved an unacceptable degree of mucosal irritation.

Analeptics

On the basis of experiments with dogs and the production of convulsions it was concluded that the sublingual/subcutaneous ratio of effective doses was 4 for strychnine and 6 for picrotoxin (7). This indicated that dangerously large doses would be required with human subjects.

Epinephrine likewise has a low degree of penetration (8). Beckman (18) states that asthmatic infants respond to sublingual doses of 1.5 milligrams of epinephrine. This could possibly mean that penetration is more readily obtained in infants.

Ephedrine, although exhibiting more promising solubility characteristics, shows its degree of penetration to be low (8).

Metrazol and hydrocyanic acid do not produce any effects in human subjects with relatively large doses (8).

Cardiac Glucosides

Strophanthin effects are not secured from tablets employed sublingually (19). Digitoxin also indicates that it would not be effective sublingually in any practical dosage (8).

Insulin

Insulin is protein in nature and hence would not be expected to exhibit favourable oil solubility. Work by McCullagh and Lewis (20) and Walton (7) demonstrated the ineffectiveness of the sublingual technique. Their observation satisfactorily refute reports which have claimed successful sublingual administration of insulin (21).

Heparin

Administration of heparin sodium from 100 mg. to 400 mg. doses produces no prolongation of clotting time to within the therapeutic range (twenty-five to thirty-five minutes) (22). Heparin sodium is soluble in water and practically insoluble in organic solvents, and thus appears to fit the earlier theory of Walton.

Mechanics of Absorption

Walton's observations (8) show that the fat-water distribution coefficient of drugs is a dominant factor in determining their penetrability through the oral mucosa. With the drugs so far studied, coefficients of approximately 20 to 30 fall in the borderline range of effective administration by sublingual application. A number of common drugs with lower coefficients have been shown to be ineffective. Some of the organic nitrates and steroid hormones have been effectively administered sublingually and their coefficients fall in the range of 40 to 2,000. This may be considered an optimum range. It is probable that drugs with coefficients higher than this range may not be effective, in which case the explanation would be that adequate concentration could not be obtained in the aqueous salivary fluids of the mouth.

Experimentally, it was found by Walton (8) that there was no special penetrability to be obtained by using the free alkaloid instead of the alkaloidal salt. It may be concluded that the salt dissociates and allows the free base to act in the mouth as it does in the in vitro oil-water system. Apparently in the mouth the same conditions of competition of solvents prevails and in this case the predominant competition is that between the aqueous salivary fluids and the fat in the protoplasm of the cells. Using the free alkaloid, solutions in water and alcohol or in water and propylene glycol were employed. Further admixture with alkalis and with surface active agents such as bile salts provided no significant improvement in penetrability. However, with desoxycorticosterone acetate which is more readily absorbed sublingually a change of solvents appears to effect the absorption. Thorn and his associates (15-c) found that with a solution of pure propylene glycol the dosage required was 3 times that of the intramuscular dose. On the other hand, Anderson *et al* (15-a) used less than twice the injected dose with a propylene glycol solution diluted with 20% absolute alochol. The former has a surface tension of 42 dynes per

square centimeter and the latter a surface tension of 31 dynes per square centimeter. Thus it would seem that hormones mixed with mucilaginous drugs and emulsifying agents which promote absorption and these compressed at high pressure to a tablet would produce a superior type administration (13-b).

The most feasible method for improving the sublingual penetrability of a given drug seems to be the preparation of chemical derivatives with more favourable solubility characteristics. Nitrate and acetate esters for instance will exhibit a significantly improved distribution coefficient, and in some cases the typical activity of the original drug can be retained or even intensified. This procedure would be most applicable in the case of those drugs which are on the borderline of effective penetrability. Thus in synthetic preparation of new drugs and in the chemical variations of the standard drugs this particular feature might be advantageously added to other objectives.

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LEARNING FOR THINKING (continued from page 69)

"The central issue is the capacity of the free society to survive in this age when those who would not scruple to destroy it ruthlessly are in command of instruments for the conditioning of the social psychology more effective than have ever before been available to those who lust for power over their fellow men. The unrest which holds all of humanity in its grip today, no matter in what social forms it may temporarily manifest itself, is basically the revolt of countless individuals against the threat of dehumanization which inheres in the ever increasing complexity which technical advance is imposing on modern society.

"If this is the situation, then there exists today a vital need, and a corresponding opportunity, for liberal education, which from its very beginnings has been concerned with the individual person as a social being. In all ages the question with which it deals is how the individual may relate himself to other individuals so that he may be free to grow in capacity to recongnize and enjoy the maximum of the personal values of life without disrupting or endangering social order."

(From an address, Learning for Thinking, by Principal William C. Graham of United College, Winnipeg, to the Classics Section of the Manitoba Educational Association, April 21st, 1954)

BOOK REVIEWS

Welch, H.; The Manual of Antibiotics; Publishers—Medical Encylopedia, Inc., 30 East 60th St., New York 22, N.Y.; Distributors, American Pharmaceutical Association, 2215 Constitution Ave., N.W., Washington, D.C.; $2.50

The number of antibiotic preparations on the market has increased greatly during the past few years. As stated in the preface of this book, one single penicillin preparation has as many as 36 trade names. No doubt many pharmacists have been confronted with the problem of determining the composition of various antibiotic products and would welcome a ready source of reference. The recently published Manual of Antibiotics should aid materially in meeting this need.

The manual contains a listing of all the presently commercially available antibiotic preparations. The book is indexed as (1) Index of Trade Names (2) Index of Generic Names (3) Index of Manufacturers. This method of indexing facilitates the finding of a particular commercial product or the various preparations of a particular antibiotic (Index of generic names). There is also at the front of the manual a listing of the antibiotics used in animal feeds with their trade names and a list of the antibiotics for diagnostic use and commercial sources. Indications for the use or uses of the various commercial prepartions are also given under each monograph.

This manual should fill the need of the pharmacist or physician for a ready source of reference on antibiotic preparations.

R. M. BAXTER

Wilson, C. O., and Grisvold, O.; Textbook of Organic Medicinal and Pharmaceutical Chemistry, 2nd. edition, J. B. Lippincott Co., Montreal, 1954. $10.00.

The Second edition of this text (used in Pharmaceutical Chemistry 31 at the Faculty of Pharmacy, University of Toronto) is a considerable improvement over the first edition (1949), reflecting not only the great advances in medicinal chemistry in the past five years, but also the views of the many teachers who used the first edition as a text. The editors express succinctly the views of many teachers when they say in the preface, "The information assembled is that which is thought to be of practical value to the present-day pharmacist, since it now is understood quite generally that a pharmacist should have a thorough knowledge of what a drug is, its limitations, applications, forms and uses, as well as of those characteristics which pertain strictly to its compounding." The method of classification of organic medicinals in this excellent book represents a compromise of chemical (i.e. knowledge of physical and chemical properties) and pharmacological (i.e. knowledge of physiological activity or medicinal use). In the experience of the writer, this is an ideal approach to this tremendously important material.

The facts that over 80% of to-day's prescriptions concern ethical specialties and that 90% of these concern organic drugs, indicate very definitely the usefulness of this book in the library of every practising pharmacist. It is available from the University of Toronto Book Store.

G. R. PATERSON

AN AMPLER AND ROUNDED EDUCATION

"Democracy is the view that not only the few but that all are free, in that everyone governs his own life and shares in the responsibility for the management of the community. This being the case, it follows that all human beings stand in need of an ampler and rounded education. The task of modern democracy is to preserve the ancient ideal of liberal education and to extend it as far as possible to all the members of the community. In short, we have been apt to confuse accidental with fundamental factors, in our suspicion of the classical ideal. To believe in the equality of human beings is to believe that the good life, and the education which trains the citizen for the good life, are equally the privilege of all. And these are the touchstones of the liberated man: first, is he free; that is to say, is he able to judge and plan for himself, so that he can truly govern himself? In order to do this, his must be a mind capable of self-criticism; he must lead that self-examined life which according to Socrates is alone worthy of a free man. Thus he will possess inner freedom, as well as social freedom. Second, is he universal in his motives and sympathies? For the civilized man is a citizen of the entire universe; he has overcome provincialism, he is objective, and is a 'spectator of all time and all existence'. Surely these two are the very aims of democracy itself."
(General Education in a Free Society: Report of the Harvard Committee. 1945)

ACCOUNTING FOR PHARMACY STUDENTS

This new accounting text by H. J. Fuller, Associate Professor of Pharmacy in charge of Pharmacy Administration, University of Toronto, Faculty of Pharmacy, presents in succinct fashion the bookkeeping procedures and accounting principles necessary for the successful operation of a retail pharmacy. The chapter headings are as follows:

1. Basic Concepts.
2. Accounts Showing Changes in Earned Surplus.
3. Journalizing and Posting.
4. Working Papers—Closing the Books.
5. Merchandise Accounts.
6. Special Books of Original Entry.
7. Cash Discounts—Freight In—Freight Out—Expenses.
8. Controlling Accounts.
9. Promissory Notes—Bills of Exchange.
10. Reserves for Bad Debts and Depreciation.
11. Departmentalization of Records.
12. Individual Proprietorship—Partnership.
13. Miscellaneous—Purchase Book—Payroll Summary.

Laboratory material follows each chapter and can be easily removed from the text. The book is available from the University of Toronto Press, Book Store, $7.50 postpaid. As part of the Extension Services of the Ontario College of Pharmacy, Professor Fuller will check and return the problems to any pharmacist wishing to avail himself of this opportunity to improve his accounting procedure.

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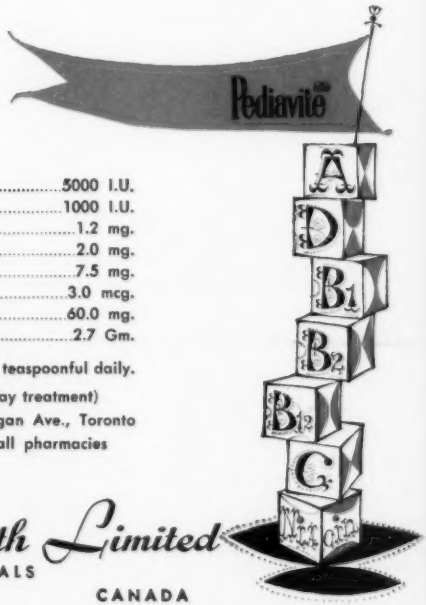
POTENCY ASSURED in new

Pediavite

E.B.S.

FOR CHILDREN . . .

Potency of vitamins in Pediavite is assured because they are dispersed in a dry, dextrose base. In addition, Vitamins A & D have been given a special stabilization process. Pediavite is a palatable, vitamin preparation which dissolves readily in the child's formula, in a glass of milk or orange juice, or spread on cereal or other food.



Contains per level teaspoonful:

Vitamin A.	5000 I.U.
Vitamin D.	1000 I.U.
Thiamin Mononitrate	1.2 mg.
Riboflavin	2.0 mg.
Niacinamide	7.5 mg.
Vitamin B_{12}	3.0 mcg.
Ascorbic Acid	60.0 mg.
Dextrose	2.7 Gm.

Suggested Dosage: One level teaspoonful daily.

Package: 3 oz. jar (30 day treatment)

Write for sample to 525 Logan Ave., Toronto

Available by ℞ . . . at all pharmacies

E. B. Shuttleworth Limited

PHARMACEUTICALS

TORONTO CANADA